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Mini Review

# Can Next Generation Genomics be Used to Predict the Outcome of Total Joint Arthroplasty

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**Abbreviations:** IFIT: Interferon Induced Genes; TJA: Total Joint Arthroplasty; TKA: Total Knee Arthroplasty; THA: Total Hip Arthroplasty; AL: Aseptic Loosening; UHMWPE: Ultra High Molecular Weight Polyethylene; DNA: Deoxyribo Nucleic Acid; PCR: Polymerase Chain Reaction; BLAST: Basic Local Alignment Search Tool; AIR: Adverse Immune Reaction; ROS: Reactive Oxygen Species; DAMPs: Damage-Associated Molecular Patterns; GWAS: Genome-Wide Association Study; PRS: Polygenic Risk Score

## Introduction

Genomics is changing our perspective of disease processes. Events such as orthopaedic implant loosening have historically been poorly understood at a molecular level, but next generation techniques are being developed offering unprecedented insight into its root causes. Aseptic loosening decades after implant surgery has become accepted as a normal response to particulate wear debris, but premature aseptic loosening has been associated with a variant in the Interferon Induced Genes (IFIT). Evidence that early aseptic loosening is a predictable pathological process supports a preoperative genomic assessment of risk, and preemptive treatment of susceptible patients [1].

## Arthroplasty

Hip and knee osteoarthritis are among the most common musculoskeletal conditions, affecting about one in three Australians. The gold standard of treatment for advanced disease is joint replacement, about 85000 of which are performed annually in Australia alone [2]-worldwide numbers are now estimated in the millions and are projected to increase dramatically in the near future as lifestyle factors interplay with improving access to health services [3]. There is an inherent failure rate in Total Joint Arthroplasty (TJA) of about 5% at 10 years, with more than 8000 implants revised in Australia in 2017, increasing over the years along with primary procedures [2]. Primary arthroplasty procedures in Australia have been modelled to increase by 276% for Total Knee Arthroplasty (TKA) from 2018 to 2030 and 208% for Total Hip arthroplasty (THA) [4]. The most common indication for revision TJA is Aseptic Loosening (AL), making up about 25% of the revision burden [2]. Although a drastic design improvement in the form of highly cross-linked Ultra High Molecular Weight Polyethylene (UHMWPE) liners has brought about a reduction from about 40% of the revision burden in recent years, AL still leads to very large numbers of revision procedures which incur

morbidity, mortality and significant cost [2,5]. Revision TJA is more complex, more time consuming, has poorer outcomes and higher complication rates than primary procedures [2,5]. In addition to this, significantly more expensive implants and longer hospital stays contribute to greatly increased costs, generally incurring about twice the expenses of a primary TJA procedure [5].

## Genomics

Recent advances in the fields of genetics, molecular biology, biochemistry and bioinformatics have led to the rise of a field of science known as genomics-an interdisciplinary field of biology focusing on the collective characterisation of the entire genome of an organism [6]. Whereas genetics traditionally focuses on individual genes, genomics considers the full genome and its complex interrelations and influences on the organism as a whole. It is only in recent years with the advent of supercomputers that the human genome, consisting of over three billion base pairs and 20,000 genes, can be comprehensively studied and sequenced, this giving rise to unprecedented possibilities. A full genome can now be sequenced for a few thousand dollars, enabling personalised and specific genetic diagnostics and tailored therapies. As analysis matures, implications are being identified reaching across all fields of medicine. Despite unprecedented access to the human genome, this is only part of the picture. Parallel advances in quantitative RNA expression and phenomics have enabled 3 tier "omics" data sets to provide functional confirmation of genomic coding .

## History

The history of genomics begins naturally in genetics. Mendel described the original units of inheritance [7] and the chromosomal theory of inheritance was proposed by Sutton & Boveri in 1902 [8,9]. The Deoxyribo Nucleic Acid (DNA) double helix was described in 1953 by Watson & Crick [10] followed closely by the correct identification of the 46 human chromosomes in 1956 by Tjio [11]. During the 1970s the sanger group at cambridge sequenced the first complete genomes of viruses and mitochondria in a major leap forward [12]. Automated DNA sequencing and Polymerase Chain Reaction (PCR) was developed in the early 1980's [13] and allowed DNA amplification on new scales from small samples, vastly increasing the speed and ease with which genetic material could be studied and replicated. During the 1990s technology advanced to a point where the Human Genome Project could be undertaken, an international research collaboration with the aim of mapping the entire human genome and its function. The project was successfully completed and published in 2003, forming modern genomics in the process at a cost of about $3 billion USD [14]. Today genome sequencing costs around $2000 USD per individual. It is now possible for humans to have their entire genomes examined for detailed information on heraldry, genetic errors, hereditary disorders but also genetic predispositions to developing a multitude of diseases including cancer, dementia and autoimmune disorders. This in itself is leading to targeted screening, preventative measures and even tailored genetic therapies addressing and altering the relevant genes. Needless to say, the future implications are enormous.

## Modern Genomics

Gene expression analysis is one of the modern processes enabling advanced genomics. Gene expression is the process by which genetic code is translated into functional products. DNA strands are constructed from nucleotides, monomer base units of Adenine, Thymine, Cytosine and Guanine attached to a sugar-phosphate backbone (Deoxyribose in DNA, Ribose in RNA). RNA utilises Uracil in the place of Thymine. The RNA Polymerase enzyme reads DNA sequences and produces RNA from the specified code in a process known as transcription. RNA broadly plays roles in synthesis, regulation and processing of proteins. Several types of RNA occur depending on the function of the gene. Genes that encode proteins produce messenger or mRNA, which determines the sequence of the protein products of genes. Proteins are then produced from mRNA code in a process known as translation. Regulation of gene expression can occur at several stages, including transcription, RNA splicing, translation and post-translational modification. Gene regulation enables cells to undergo differentiation, morphogenesis and enables alterations in structure and function. Analysis of gene expression has evolved into a very important strategy in fields such as oncology, where alterations are frequently implicated in disease processes [6]. mRNA and protein analyses are useful in comparing patterns of tumour gene expression with normal tissues, and in the same way can be used to delineate differences between individual responses to foreign material. Methods used in comparative gene expression analysis include gel electrophoresis, which was responsible for the discovery of the p53 tumour suppressor protein [15]. This later evolved into mRNA expression analysis, utilising complementary DNA strands to match selected RNA sequences [16]. This method uses hybridisation pattern comparison and allows identification of gene expression differences between samples. During the 1990s a technique called differential display integrated PCR and DNA sequencing by gel electrophoresis [17].

Automated DNA microarray analysis has been arguably the most important advance in recent years and allows for automated measurements of gene expression in large numbers of genes simultaneously, enabling massive parallel mining of biological data with expression monitoring, polymorphism detection and genotyping on a whole genome scale [6,18]. The technology has in fact advanced to a point where the data sets become massive on a scale which poses a challenge to contemporary computer technology. Microarray technology now permits analysis of molecular pathways and identification of mechanisms conferring drug resistance, autoimmune processes and complex cancer genetics providing targets for identification by lab testing and enabling personalised therapeutic intervention [6]. Essentially, this level of insight into pathology, progression, resistance to treatment, and response to cellular microenvironments can guide early diagnosis and innovative therapeutic approaches. Bioinformatics is the science of biological data sets, which require specialized technology in order to manage the vast amounts of information produced in the analysis of whole genomes. Methods such as

Basic Local Alignment Search Tool (BLAST) enable sequenced genetic material to be annotated (labelled) and searched, allowing comparisons between different samples and organisms utilising vast databases [19]. Efficiency can be vastly improved by the recent concept of selectively sequencing the Exon regions of DNA . These are the sequences which are transcribed into mature RNA and make up only about 1% of the genome. Exon sequencing avoids the labour of sequencing the non-coding regions, thereby producing a selective data set known as the exome, now available commercially for a few hundred dollars [6]. Metabolomics is a burgeoning field which considers the downstream 'omics' tier of metabolite products of proteins [20]. Proteomics concerns the protein products of translation and transcriptomics the mRNA transcription products. By studying metabolites at a systemic scale and integrating this tier with proteomic and transcriptomic datasets, cutting edge programs are now able to connect and visualise cascades of molecular structure and function from the genetic code level to the resultant metabolic processes. The stepwise generation of phenotypes from DNA as well as the influences of upstream factors can therefore be studied and catalogued [21]. Su, et al. [22] were recently able to identify meaningful gene-metabolite associations including abnormal relationships directly linked to known gene mutations in cancer cell lines using the collaborative NCI-60 dataset, showing how a multi-tier omics approach is allowing us visualise the big picture in biological consequences of genetic code.

## Applications in Arthroplasty

Aseptic loosening is a multifactorial process, however there is good evidence to suggest that one of the root causes is an Adverse Immune Reaction (AIR) based on chronic antigen-specific immune activation involving the B7-CD28 pathway [23] Metal-on-metal articulations are known to cause a lymphocyte-dominated immune response to microscopic wear debris that eventually leads to AL [24] and further studies have identified a link between innate immune system activation via toll-like receptors and development of loosening [25] Polyethylene debris similarly triggers an innate immune response and activates periprosthetic inflammation predisposing to loosening [26]. According to present consensus, wear debris induces a multifaceted immune response which generates Reactive Oxygen Species (ROS) and Damage-Associated Molecular Patterns (DAMPs) [27]. Only a few studies have addressed the role of genetic variability in the development of AL. Malik, et al. [28] identified several genetic variants known as single nucleotide polymorphisms (a substitution in a single nucleotide of DNA) in the OPG and RANK genes which were found to be associated with AL [28]. Further research has identified positive associations between genes including MBL, MMP-1 and VDR genes [1,29]. Further high-quality research is urgently needed in these areas. In addition to germ line DNA variations we know that the RNA transcriptome (the set of all RNA produced by a specified population of cells) changes in the tissues surrounding implants. These changes are not always identifiable remotely from systemic analysis by blood sample and necessitate localised tissue sampling. Transcriptome analysis can be used to identify the specific genetic activity in a population of cells and therefore trace back the changes that occur in the tissues of interest, as well as target specific therapies isolating messenger and structural molecules. In a recent study by Koks et al. several genetic markers relating to genetic variants have been identified which strongly correlate with the longevity of TJA implants and have therapeutic potential. This was a proof of concept study which developed clinical analysis protocols and identified potential genetic markers, forming a solid foundation for a large future cohort study. 420 subjects across Estonia and Germany were enrolled and examined using Genome-Wide Association Study (GWAS) and Genechip gene expression analysis. This preliminary study successfully identified 53 SNPs significantly associated with AL at loci in chromosomes 2, 9, 14 and 22. The highest odds ratio for AL was 21.6, identified in relation to the IFIT2, 3 genes [30].

Larger sample sizes and a multidisciplinary approach will be required to study AL and its underlying cellular processes comprehensively, but the stage has been set. In order to understand, address and ideally prevent the biological fundamentals of AL, we have designed a collaborative project which will compare matched patients with and without implant loosening in terms of genetic markers and transcriptome profiles. This information will enable development of a Polygenic Risk Score (PRS) relating to different implant materials, permitting pre-surgery planning including implant selection and fixation methods on an individual basis. Genomics tools have become highly standardized and widely available but have yet to reach practical incorporation into clinical practice and we are only scratching the surface of the potential hidden in these tiers of coding. This untapped technology offers straightforward analytical pathways to identify genetic variants and their functional consequences in the pathogenesis of diseases. The information is highly complex, but we are now in possession of advanced computing and bioinformatics techniques to match. Combination of genomics, transcriptomics, proteomics and metabolomics into a unified multiomics approach has until recently been prohibitively complicated but new technology is enabling us to meet the unmet need to combine these fields with clinical information in new and exciting approaches. Next generation genomics will significantly improve our ability to predict clinical outcomes and guide our decision making in diagnostic and therapeutic options alike. Orthopaedics stands as a potential trailblazer in this development with the opportunity of combining genotype profiles with prosthetic system outcomes, enabling personalized decision-making. The sooner we utilise the massive potential of this technology into clinical workflows the more improvements we stand to make in patient outcomes, developing entirely new standards of treatment. Genomics has arrived in the surgical sphere and it is here to stay.

## References

1. Godoy-Santos AL, D'Elia CO, Teixeira WJ, Cabrita HB, Camanho GL (2009) Aseptic loosening of total hip arthroplasty: Preliminary genetic investigation. The Journal of Arthroplasty 24(2): 297-302.

2. Australian Orthopaedic Association National Joint Replacement Registry (AOANJRR) (2018) Hip, Knee & Shoulder Arthroplasty Annual Report. pp. 1-444.

 

3. Kurtz S, Ong K, Lau E, Mowat F, Halpern M (2007) Projections of primary and revision hip and knee arthroplasty in the United States from 2005 to 2030. The Journal of Bone and Joint Surgery American 89(4): 780-785.
4. Ackerman IN, Bohensky MA, Zomer E, Tacey M, Gorelik A, et al. (2019) The projected burden of primary total knee and hip replacement for osteoarthritis in Australia to the year 2030. BMC Musculoskeletal Disorders 20(1): 90.
5. Weber M, Renkawitz T, Voellner F, Craiovan B, Greimel F, et al. (2018) Revision surgery in total joint replacement is cost-intensive. Biomed Research International, pp. 8987104.
6. Jones R, Wood D (2013) Sarcoma genomics. Bone & Joint 360 2(6): 2-8.
7. Mendel G (1866) Negotiations of the Natural Research Association in Brno. Experiments on Plant Hybrids, Association's Publishing House, France, 4: 3-47.
8. Sutton W (1903) The chromosomes in heredity. Biological Bulletin 4: 231-251.
9. Boveri T (1904) Results on the constitution of the chromatic substance of the cell nucleus. Germany.
10. Watson JD, Crick FHC (1953) Molecular structure of nucleic acids: A structure for deoxyribose nucleic acid. Nature 171: 737-738.
11. Tjio JH, Albert Levan (1956) The chromosome number of man. Hereditas 42(1-2): 1-6.
12. Sanger F, Air GM, Barrell BG, Brown NL, Coulson AR, et al. (1977) Nucleotide sequence of bacteriophage phiX174 DNA. Nature 265(5596): 687-695.
13. Saiki RK, Gelfand DH, Stoffel S, Scharf SJ, Higuchi R, et al. (1988) Primer-directed enzymatic amplification of DNA with a thermostable DNA polymerase. Science 239(4839): 487-491.
14. Lander ES, Linton LM, Birren B, Nusbaum C, Zody MC, et al. (2001) Initial sequencing and analysis of the human genome. Nature 409(6822): 860-921.
15. Matlashewski G, Lamb P, Pim D, Peacock J, Crawford L, et al. (1984) Isolation and characterization of a human p53 cDNA clone: Expression of the human p53 gene. EMBO J 3(13): 3257-3262.
16. Sargent TD (1987) Isolation of differentially expressed genes. Methods Enzymol 152: 423-432.
17. Liang P, Pardee AB (1992) Differential display of eukaryotic messenger RNA by means of the polymerase chain reaction. Science 257(5072): 967-971.
18. Pollack JR, Perou CM, Alizadeh AA, Eisen MB, Pergamenschikov A, et al. (1999) Genome-wide analysis of DNA copy-number changes using cDNA microarrays. Nat Genet 23(1): 41-46.
19. Benson DA, Karsch-Mizrachi I, Clark K, Lipman DJ, Ostell J, et al. (2014) GenBank. Nucleic Acids Res 40: 32-37.
20. Cambiaghi A, Ferrario M, Masseroli M (2017) Analysis of metabolomic data: Tools, current strategies and future challenges for omics data integration. Briefings in Bioinformatics 18(3): 498-510.
21. Kuo T, Tian T, Tseng YJ (2013) 3Omics: A web-based systems biology tool for analysis, integration and visualization of human transcriptomic, proteomic and metabolomic data. BMC Syst Biol 7:
22. Su G, Burant CF, Beecher CW, Athey BD, Meng F, et al. (2011) Integrated metabolome and transcriptome analysis of the NCI60 dataset. BMC Bioinformatics 12(1): 36.
23. Farber A, Chin R, Song Y, Huie P, Goodman S (2001) Chronic antigen-specific immune-system activation may potentially be involved in the loosening of cemented acetabular components. Journal of Biomedical Materials Research 55(3): 433-441.
24. Willert HG, Buchhorn GH, Fayyazi A, Flury R, Windler M, et al. (2005) Metal-on-metal bearings and hypersensitivity in patients with artificial hip joints. A clinical and histomorphological study. The Journal of Bone and Joint Surgery American 87(1): 28-36.
25. Pajarinen J, Jamsen E, Konttinen YT, Goodman SB (2014) Innate immune reactions in septic and aseptic osteolysis around hip implants. Journal of Long-Term Effects of Medical Implants 24(4): 283-296.
26. Veruva SY, Steinbeck MJ, Toth J, Alexander DD, Kurtz SM (2014) Which design and biomaterial factors affect clinical wear performance of total disc replacements? A systematic review. Clinical Orthopaedics and Related Research 472(12): 3759-3769.
27. Cobelli N, Scharf B, Crisi GM, Hardin J, Santambrogio L (2011) Mediators of the inflammatory response to joint replacement devices. Nature Reviews Rheumatology 7(10): 600-608.
28. Malik MH, Bayat A, Jury F, Ollier WE, Kay PR (2006) Genetic susceptibility to hip arthroplasty failure--association with the RANK/OPG pathway. International Orthopaedics 30(3): 177-181.
29. Malik MH, Bayat A, Jury F, Kay PR, Ollier WE (2007) Genetic susceptibility to total hip arthroplasty failure--positive association with mannose-binding lectin. The Journal of Arthroplasty 22(2): 265-270.
30. Final Report Summary-HYPORTH (2013) New approaches in the Development of Hypoallergenic Implant Material in Orthopaedics: Steps to Personalised Medicine. Germany.